International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 5 Issue 4, May-June 2021 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Potential of Natural Compounds in Treating Breast Cancer

Komal Kaushik, Gunjan Choudhary, Akanksha, Vandana, Shweta Tyagi, Abhimanyu Kumar Jha

Department of Biotechnology, Faculty of Life Sciences,
Institute of Applied Medicines and Research, Ghaziabad, Uttar Pradesh, India

ABSTRACT

Breast cancer is the most frequently diagnosed cancer; it has been treated for a long time with hormonal, medical assistance, surgery, chemotherapy, and irradiation. Natural compounds obtained for living organisms facilitate caspase mediated cell death and inhibit metastasis, so cancer growth is often prevented with greater efficacy. These compounds are often found to slow the progression of breast cancer. They improved patient survival rates and minimized the number of deaths caused by breast cancer. Apoptosis is defined as the death of cells that occurs as a natural and controlled part of an organism's growth or development. The production of membrane-enclosed apoptotic bodies with well-preserved organelles, as well as rapid cell condensation and budding. Within the process, there are certain morphological changes. The most important indicator of apoptosis induction is the presence of Cytotoxic anticancer agent. Some plant and natural chemicals promote apoptosis, which obstruct cancer cells through a variety of processes.

KEYWORDS: *Breast cancer, apoptosis pathway, natural compounds*

How to cite this paper: Komal Kaushik | Gunjan Choudhary | Akanksha | Vandana | Shweta Tyagi | Abhimanyu Kumar Jha "Potential of Natural Compounds in Treating Breast Cancer" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-5 | Issue-4, June 2021, pp.820-824, URL: www.ijtsrd.com/papers/ijtsrd42410.pdf

IJTSRD42410

INTRODUCTION

Breast cancer could be a major public health issue on a global scale (Li et al., 2017). It's the second most commonly diagnosed cancer, and it's also a leading cause of mortality in women around the world (Struck et al., 2018). It progresses into foetal illness, with risk factors that are similar to those of breast cancer (Siegel et al., 2018).The number of external and intracellular substances can cause BrCa pathology, which can make the condition worse (Kamaruzman et al., 2018). Chemotherapy, surgery, and hormone therapy are examples of conventional treatments that have adverse effects and are the most commonly used way for breast cancer treatment (Chen et al., 2015).Multidrug resistance (MDR) is one of the most worrisome concerns with conventional treatment. It is used to treat patients with breast cancer (Singh et al., 2017, Ouyang et al., 2014).They have unpredictably negative side effects while also assisting treatment. Nausea, vomiting, neuropathy, constipation, diarrhea, and difficulties breathing are all typical side effects. Treatments for breast cancer are needed by medical professionals. Chemotherapy medications must be replaced with natural chemicals to avoid significant adverse effects and drug efflux (Ouyang et al., 2014). Natural substances are the greatest treatment for breast cancer since they work on multiple targets and have no adverse effects. Natural substances have been proven to be the safest, fastest, cheapest, and least toxic in the treatment of breast cancer (Mitra et al., 2018; Ijaz et al., 2018). A number of these chemicals cause apoptosis as a result of chemo sensitization (Aung et al.,2017).

Natural compounds

Quercetin

Quercetin (QC) is a flavonol found in plants such as *Allagopappus viscosissimus, Opuntia ficus-indica var. saboten, Lychnophora staavioides,* and *Rhamnus* species (Aghapour et al., 2018; Li et al., 2013). This compound can be found in a variety of vegetables, fruits, wine, tea, and other foods (Manouchehri et al., 2018).

Anticancer, antioxidant, antitumor, and anti-inflammatory properties are all present (Parts et al., 2018). Quercetin promotes a healthy cell type in prostate, lung, breast, colon, and cervical cancers (Manouchehri et al., 2018). QC inhibits the expression of antiapoptotic proteins including BAD and BAX, which facilitate cancer cell apoptosis (Manouchehri et al., 2018).Compounds containing quercetin may be a potential therapeutic for treating multiple cancers by causing cancer cells to apoptosis (Wang et al., 2018) for breast cancer prevention and therapy (Aghapour et al., 2018). Quercetin may have various properties that are beneficial to the ability and expansion of BrCa somatic cells (MDA-MB-231).Since the proliferation of breast cancer cells is inhibited by quercetin, it has anticancer properties (Wang et al. , 2018). The inhibition of intracellular signaling pathways such as P13k, EGFR, and Her2/neu by quercetin results in the induction of neoplastic cell caspase-mediated cell growth (P53, BCL-2 family, FasL) and thus the suppression of neoplastic cell proliferation (Nguyen et al., 2017). Quercetin's anti-proliferative effects in human phenobarbitone steroid receptor positive MDA-MB -453 TNBC cells are mediated by an increase in BAX expression

and a decrease in Bcl-2 expression via G2/M cell cycle arrest and caspase-mediated cell death (Choi et al., 2008).Quercetin treatment increased the level of translocation, protein or proapoptotic Foxo3a, and transcriptional activity in MDA-MB-231 cells, which in turn triggered the necrobiosis system, p53, p21, and GADD45 signalling (Nguyen et al., 2017).Quercetin treatment causes S Phase G2/M cell cycle, which is associated with pro-apoptotic events that decrease viability and induce apoptosis (Nguyen et al.,2017).

Tetrandrine

Tetrandrine has anti-proliferative and anti-tumor properties. *Stephania tetrandra*, an Asian herb (Chinese plant) used for medical purposes, may contain a benzyl tetrahydroisoquinoline alkaloid (Lan et al., 2018). Natural compounds have pro-apoptotic effects on cancers such as leukemia, melanomas, prostate cancer, and breast cancer (Lan et al., 2018). Tetrandrine's pharmacological properties include the blocking of positive ion channels and the blocking of several drug resistance proteins (Xu et al., 2011). Tetrandrine affects tumor cell resistance and reverses drug resistance in human BrCa cells (Chen et al., 2013), and is used to treat a variety of cancers (Jiang et al., 2017). Tetrandrine inhibits the growth of cancer cells, making it a promising agent for studying different cancers. It kills inflammatory and breast cancer-initiating cells, preventing their development (Wong et al., 2017). Tetrandrine has pro-autophagic effects on a variety of BrCa cell lines, promotes necrobiosis in cells, and acts as an autophagy activator. Tetrandrine reverses tamoxifen drug resistance. Because of autophagy apoptosis resistance cell lines that have a low expectation of proteolytic enzyme caspase 3,caspase 7,and BAX, Bak necrobiosis once treated with Tetrandrine, Tetrandrine is proof against cell death (Wong et al., 2017).

Curcumin

Curcumin promotes somatic cell regeneration and signaling. It's possible that the yellow colour in turmeric comes from a plant-derived polyphenol. This pigment is derived from the curcuma longa plant (turmeric) and is thought to have anti-cancer properties (Sa et al., 2008).It has anticarcinogenic effects on epithelial cell carcinomas and on respiratory organs, breast, pancreatic, brain, head and neck large intestine, and it has anti-inflammatory, anti-tumour, anti-microbial, and anti-oxidative properties (Jung et al., 2018, Ferreira et al., 2015,Liu et al., 2013,Zang et al., 2014).It prevents cancer cells from surviving, growing, or migrating invasively (Coleman et al., 2015). CUR has the fewest side effects of any chemotherapeutic drug (Jung et al., 2018). It has the makings of a promising agent for the treatment of a variety of cancers. Wnt signalling is inhibited by curcumin in MCF7 cells, which are dysregulated in breast cancer (Lindvall et al., 2007,Liu et al., 2005).This route is important for breast vegetative cell self-renewal, and it also has epigenetic activity when inhibited. Curcumin inhibits NF-KB expression while also increasing the efficacy of paclitaxel. In MDA MB-231(ER-/PR-)cells, this combination outcome reduces breast cancer growth. Curcumin decreases the dimension of cell proliferation and tumour with improved the speed of apoptosis, and it integrates medical of paclitaxel and downregulates MMP-9 expression (Aggarwal et al., 2005).The repressive activity of tetrahydro curcumin on ATP-binding container (ABC) drug transporter P- conjugated protein (ABCB1/P-gP), multidrug resistance supermolecule 1(ABCC1), and mitoxantrone resistance supermolecule (ABCG2/MXR) throughout that established that curcumin may be a chemosensitizer and its act against drug resistance.

Thymoquinone

Thymoquinone (TQ) is found in the seeds of nigella sativa (Black caraway). TQ compounds fight malignancies such as leukemia, pancreatic adenocarcinoma, osteosarcoma, laryngeal cancer, ovarian cancer, liver cancer, breast cancer, prostate cancer, and colorectal cancer (Bhattacharya et al., 2015, Dehghani et al.,2015, Motaghed et al., 2013, Odeh et al., 2012, Woo et al., 2013). Many targets are involved in anticancer action for TQ, including p53, p73, STATE3, NK-kB, PPAR-, and ROS (Woo et al., 2013). Thymoquinone increases the quantitative relationship between BAX and BCL-2 in MCF7, HCT-116, and HL-60 cancer cells. It increases the amount of pro-apoptotic macromolecules, lowering the amount of anti-apoptotic proteins, and demonstrating anti-proliferative properties (Motaghed et al., 2013). Thymoquinone may be a promising cancer therapy chemical. By signalling increased phosphorylation of p38 and ROS, it has anti-migratory and pro-apoptotic characteristics against breast cancer cells. Thymoquinone is an effective treatment for BrCa, as evidenced by the downregulation of anti-apoptotic proteins, the encouragement of p38 phosphorylation, and the reduction in the size of breast tumours (Woo et al., 2013) The tumour spreads by altering the cell cycle and targeting NF-kB. Thymoquinone is an effective breast cancer treatment that promotes apoptosis in BrCa cells. During a decline phase, thymoquinone promotes cleavage of the poly (ADP-ribose) enzyme, which leads to an increase in H2AX, AKt phosphorylation and, as a result, downregulation of the production of X-ray linked apoptosis inhibitors (Sutton et al., 2004). PPAR- and its inhibitors stop MCF-7/DOX cells from proliferating (Woo et al., 2011). Thymoquinone also inhibits cyclin D1 and cyclin E production, as well as AKt, by phosphorylating 4E-BP1, elF4E, S6R, and P70S6K (Rajput et al., 2013).

Resveratrol

Resveratrol (trans-3,5,4'-trihydroxystilbene, RES) is an anticarcinogenic polyphenolic substance generated from a plant. It's found in grapes, berries, Pomegranate, peanuts, and soybeans, and has been recognized as a strong anti-aging, anti-inflammatory, and chemoprevention drug against a variety of molecular targets (Athar et al., 2009, Savoured et al., 2009).

RES suppresses tumour growth by inducing apoptosis in tumour cells and activating cell cycle arrest for the prevention and treatment of a variety of diseases. This chemical alters the genetic and epigenetic profiles of cells with malignancies, as well as their anticancer characteristics (Kala et al., 2015). Inflammation, leukaemia, and viruses are all suppressed by it. RES triggers apoptosis in cells via targeting p53, Rb, and cell cycle kinase (Carter et al., 2014). RES demonstrates multi-target efficacy, medical safety, and prize efficacy. RES has developed a therapy approach for a variety of malignancies (Vinod et al., 2015). MDA-MB-231 and MDA-MB-231/PACR, triple negative BrCa cell lines, initiate apoptosis, promote senescence, and limit cell proliferation through RES. It also activates caspase 7 in the process of inducing apoptosis (Sprouse et al., 2014). Its regulation of BCL-2 slows the growth of malignancy. Resveratrol enhances p53 expression, inhibits procaspase 8, and activates caspases seven and nine (Casanova et al. 2012). So far, breast cancer has been successfully treated. Resveratrol has the potential to be a useful agent.

Genistein

Genistein, an isoflavone phytoestrogen found in Leguminosae (fabaceae), has anticancer effects on a variety of malignancies (Fan et al., 2013). reduce the incidence of various cancers using dietary components that have a possible and major effect in it (Sarkar et al., 2003).

Tumors, disease, and osteoporosis are all prevented by Genistein. It also prevents the signaling pathway's epidermal protein from being activated. It has antioxidant, anti-proliferative, and anti-cancer properties, as well as suppressing ontogeny, apoptosis, and metastasis (Li et al., 2003, Latocha et al., 2014). Genistein is an effective preventative and therapeutic medication for breast cancer.

Genistein binds to the chemical change domain of DNMTI and prevents hypermethylation DNA methylation from binding to the promoter region of a variety of growth suppressor genes (TSGS), dyssynergia telangiectasia mutant (ATM), adenomatous polyposis coli (APC), enzyme, and tensin homologue (PTEN). TSGs interact with the chemical process to unregulate informative RNA expression (Xie et al., 2014). Before advocating the use of Genistein in breast cancer therapy, more clinical study will be required. Genistein treatment inhibited cell proliferation and induced apoptosis in MDA-MB-231 TNBC cells in a dose and time dependent manner (Pan et al., 2012). The increase of cells in the G2/M phase of the cell cycle is caused by genistein (Pan et al., 2012). Treatment with genistein causes a concentration-dependent suppression of MEK5, total ERK5, and phospho-ERK5 levels, as well as a reduction in NF-KB/p65 protein levels and therefore the desoxyribonucleic acid (DNA) binding activity of NF-KB, cell growth inhibition, and necrobiosis induction (Li et al., 2008).Treatment of T47D cells with a low dose of Genistein increased cell proliferation by 135 percent. The highest concentration of Genistein (125-100 M) resulted in 20-40% necrobiosis (Rajah et al, 2009).

Conclusion

Natural chemicals generated from living creatures have been proposed as a possible technique for treating breast cancer. Natural chemicals have a variety of effects on diverse targets, including reversing the effects of drug resistance and even providing therapeutic advantages. Current understanding about breast cancer treatment is recognized, including natural chemical absorption, bioavailability, information, progression, and knowledge of genetic changes, diagnostic markers and targets Several studies have shown that natural substances can inhibit carcinogenesis and reverse cancer growth by inducing necrobiosis (apoptosis) and cell cycle arrest. They impede the growth of cancer cells via altering necrobiosis pathways, as well as external and intrinsic apoptotic and autophagic pathways; these chemicals do not have significant ototoxic effects on normal cells. They need little toxicity and have a variety of anticancer and apoptotic actions. Natural chemicals are now being used in clinical practice to treat a variety of ailments. Because natural compounds have been found to have anti-cancer properties, many substances will likely be used to treat disease.

Finally, natural chemicals are only a small portion of the many substances that appear to have anti-breast cancer properties. These compounds are bringing scientists one step closer to an effective treatment for breast cancer. They must have the ability to extend the lives of patients all over the world and reduce the number of breast cancer-related fatalities. As a result, natural chemicals are commonly regarded as a therapy for treating breast cancer.

Acknowledgment

The authors acknowledge the help provided by Department of Biotechnology, Faculty of Life sciences, Institute of Applied Medicines and Research, Ghaziabad, India.

Conflict of Interest

The authors declare that there is no conflict of interest.

Reference

[1] Li Y, Li S, Meng X, Gan RY, Zhang JJ and Li HB: Dietary Natural Products for Prevention and Treatment of Breast Cancer. Nutrients, 9(7). 2017.DOI: 10.3390/nu9070728

[2] Strunk MA, Zopf EM, Steck J, Hamacher S, Hallek M and Baumann FT: Effects of Kyusho Jitsu on Physical Activity-levels and Quality of Life in Breast Cancer Patients. In vivo, 32(4), 2018. 819–824 DOI:10.21873/invivo.11313 [PubMed: 29936464].

[3] Siegel RL, Miller KD and Jemal A: Cancer statistics, 2018. CA Cancer J Clin, 68(1), 2018. 7–30 DOI: 10.3322/caac.21442 [PubMed: 29313949].

[4] Kamaruzman NI, Tiash S, Ashaie M and Chowdhury EH: siRNAs Targeting Growth Factor Receptor and Anti-Apoptotic Genes Synergistically Kill Breast Cancer Cells through Inhibition of MAPK and PI-3 Kinase Pathways. Biomedicines, 6(3), 2018. DOI: 10.3390/biomedicines6030073.

[5] Chen L and Li CI: Racial disparities in breast cancer diagnosis and treatment by hormone receptor and HER2 status. Cancer Epidemiol Biomarkers Prev, 24(11),. 2015.1666–72 DOI:10.1158/1055-9965.epi-15-0293 [PubMed: 26464428].

[6] Singh SK, Singh S, Lillard JW Jr. and Singh R: Drug delivery approaches for breast cancer. Int J Nanomedicine, 12, 2017. 6205–6218 DOI: 10.2147/ijn.s140325 [PubMed: 28883730].

[7] Ouyang L, Luo Y, Tian M, Zhang SY, Lu R, Wang JH, Kasimu R and Li X: Plant natural products: from traditional compounds to new emerging drugs in cancer therapy. Cell Prolif, 47(6), 2014.506–15 DOI: 10.1111/cpr.12143 [PubMed: 25377084].

[8] Mitra S and Dash R: Natural Products for the Management and Prevention of Breast Cancer. Evid Based Complement Alternat Med, 2018, 8324696.2018. DOI: 10.1155/2018/8324696 [PubMed: 29681985].

[9] Ijaz S, Akhtar N, Khan MS, Hameed A, Irfan M, Arshad MA, Ali S and Asrar M: Plant derived anticancer agents: A green approach towards skin cancers. Biomed Pharmacother, 103,.2018. 1643–1651 DOI: 10.1016/j.biopha.2018.04.113 [PubMed: 29864953].

[10] Aung TN, Qu Z, Kortschak RD and Adelson DL: Understanding the Effectiveness of Natural Compound Mixtures in Cancer through Their Molecular Mode of Action. Int J Mol Sci, 18(3), 2017. DOI:10.3390/ijms18030656.

[11] Aghapour F, Moghadamnia AA, Nicolini A, Kani SNM, Barari L, Morakabati P, Rezazadeh L and Kazemi S: Quercetin conjugated with silica nanoparticles

inhibits tumor growth in MCF-7 breast cancer cell lines. Biochem Biophys Res Commun, 500(4), 860–865 (2018) DOI: 10.1016/j.bbrc.2018.04.174 [PubMed: 29698680].

[12] Li J, Zhu F, Lubet RA, De Luca A, Grubbs C, Ericson ME, D'Alessio A, Normanno N, Dong Z and Bode AM:Quercetin-3-methyl ether inhibits lapatinib-sensitive and -resistant breast cancercell growth by inducing G(2)/M arrest and apoptosis. Mol Carcinog, 52(2), 134–43 (2013) DOI: 10.1002/mc.21839 [PubMed: 22086611].

[13] Manouchehri JM, Turner KA and Kalafatis M: TRAIL-Induced Apoptosis in TRAIL-Resistant Breast Carcinoma through Quercetin Cotreatment. Breast Cancer (Auckl), 12, 1178223417749855 (2018) 10.1177/1178223417749855.

[14] Patra A, Satpathy S, Shenoy AK, Bush JA, Kazi M and Hussain MD: Formulation and evaluation of mixed polymeric micelles of quercetin for treatment of breast, ovarian, and multidrug resistant cancers. Int J Nanomedicine, 13, 2869–2881 (2018) DOI: 10.2147/ijn.s153094 [PubMed: 29844670].

[15] Wang R, Yang L, Li S, Ye D, Yang L, Liu Q, Zhao Z, Cai Q, Tan J and Li X: Quercetin Inhibits Breast Cancer Stem Cells via Downregulation of Aldehyde Dehydrogenase 1A1 (ALDH1A1), Chemokine Receptor Type 4 (CXCR4), Mucin 1 (MUC1), and Epithelial Cell Adhesion Molecule F(EpCAM). Med Sci Monit, 24, 412–420 (2018) [PubMed: 29353288].

[16] Nguyen, L.T.; Lee, Y.-H.; Sharma, A.R.; Park, J.-B.; Jagga, S.; Sharma, G.; Lee, S.-S.; Nam, J.-S. Quercetin induces apoptosis and cell cycle arrest in triple-negative breast cancer cells through modulation of foxo3a activity. Korean J. Physiol. Pharmacol. 2017, 21, 205–213.

[17] Choi, E.J.; Bae, S.M.; Ahn, W.S. Antiproliferative effects of quercetin through cell cycle arrest and apoptosis in human breast cancer mda-mb-453 cells. Arch. Pharm. Res. 2008, 31, 1281–1285.

[18] Lan J, Huang L, Lou H, Chen C, Liu T, Hu S, Yao Y, Song J, Luo J, Liu Y, Xia B, Xia L, Zeng X, Ben-David Y and Pan W: Design and synthesis of novel C14-urea-tetrandrine derivatives with potent anti-cancer activity. Eur J Med Chem, 143, 1968–1980 (2018) DOI: 10.1016/j.ejmech.2017.11.007 [PubMed: 29133049]

[19] Xu W, Debeb BG, Lacerda L, Li J and Woodward WA: Tetrandrine, a Compound Common in Chinese Traditional Medicine, Preferentially Kills Breast Cancer Tumor Initiating Cells (TICs) In vitro. Cancers (Basel), 3(2), 2274–85 (2011) DOI: 10.3390/cancers3022274 [PubMed: 24212809].

[20] Jiang M, Zhang R, Wang Y, Jing W, Liu Y, Ma Y, Sun B, Wang M, Chen P, Liu H and He Z: Reduction-sensitive Paclitaxel Prodrug Self-assembled Nanoparticles with Tetrandrine Effectively Promote Synergistic Therapy Against Drug-sensitive and Multidrug-resistant Breast Cancer. Mol Pharm, 14(11), 3628–3635(2017) DOI:10.1021/acs.molpharmaceut.7b00381 [PubMed: 28895735].

[21] Chen HY and Chen XY: (Tetrandrine reversed the resistance of tamoxifen in human breast cancer MCF-7/TAM cells: an experimental research).Zhongguo Zhong Xi Yi Jie He Za Zhi, 33(4), 488–91 (2013) [PubMed: 23841269].

[22] Wong VKW, Zeng W, Chen J, Yao XJ, Leung ELH, Wang QQ, Chiu P, Ko BCB and Law BYK: Tetrandrine, an Activator of Autophagy, Induces Autophagic Cell Death via PKC-alpha Inhibition and mTOR-Dependent Mechanisms. Front Pharmacol, 8, 351 (2017) DOI: 10.3389/fphar.2017.00351 [PubMed: 28642707].

[23] Sa G, Das T. Anti cancer effects of curcumin: cycle of life and death. Cell Div. 2008;3:14. PubMed PMID: 18834508.

[24] Jung KH, Lee JH, Park JW, Kim DH, Moon SH, Cho YS and Lee KH: Targeted therapy of triple negative MDA-MB-468 breast cancer with curcumin delivered by epidermal growth factor- conjugated phospholipid nanoparticles. Oncol Lett, 15(6), 9093–9100 (2018) DOI: 10.3892/ol.2018.8471 [PubMed:29805641].

[25] Ferreira LC, Arbab AS, Jardim-Perassi BV, Borin TF, Varma NR, Iskander AS, Shankar A, Ali MM and Zuccari DA: Effect of Curcumin on Pro-angiogenic Factors in the Xenograft Model of Breast Cancer. Anticancer Agents Med Chem, 15(10), 1285–96 (2015) [PubMed: 25991545].

[26] Liu D and Chen Z: The effect of curcumin on breast cancer cells. J Breast Cancer, 16(2), 133–7(2013)DOI:10.4048/jbc.2013.16.2.1.33 [PubMed: 23843843]

[27] Zang S, Liu T, Shi J and Qiao L: Curcumin: a promising agent targeting cancer stem cells. Anticancer Agents Med Chem, 14(6), 787–92 (2014) [PubMed: 24851881]

[28] Coleman DT, Soung YH, Surh YJ, Cardelli JA and Chung J: Curcumin Prevents Palmitoylation of Integrin beta4 in Breast Cancer Cells. PLoS One, 10(5), e0125399 (2015) DOI: 10.1371/journal.pone.0125399 [PubMed: 25938910]

[29] C. Lindvall, W. Bu, B. O. Williams, and Y. Li, "Wnt signaling,stem cells, and the cellular origin of breast cancer," Stem Cell Reviews and Reports, vol. 3, no. 2, pp. 157–168, 2007.

[30] S. Liu, G. Dontu, and M. S. Wicha, "Mammary stem cells, self-renewal pathways, and carcinogenesis," Breast Cancer Research,vol. 7, no. 3, pp. 86–95, 2005.

[31] Y. Chen, W. Shu, W. Chen, Q. Wu, H. Liu, and G. Cui, "Curcumin, both histone deacetylase and p300/CBP-specifc inhibitor, represses the activity of nuclear factor kappa B and Notch 1 in Raji cells," Basic & Clinical Pharmacology &Toxicology, vol. 101, no. 6, pp. 427–433, 2007.

[32] B. B. Aggarwal, S. Shishodia, Y. Takada et al., "Curcumin suppresses the paclitaxel-induced nuclear factor-?B pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice," Clinical Cancer Research, vol. 11, no. 20, pp. 7490–7498, 2005.

[33] Bhattacharya S, Ahir M, Patra P, Mukherjee S, Ghosh S, Mazumdar M, Chattopadhyay S, Das T, Chattopadhyay D and AdhikaryA: PEGylated-thymoquinone-nanoparticle mediated retardation of breast cancer cell migration by deregulation of cytoskeletal actin polymerization through miR-34a. Biomaterials, 51, 91–107 (2015)

DOI:10.1016/j.biomaterials.2015.01.007 [PubMed: 25771001].

[34] Dehghani H, Hashemi M, Entezari M and Mohsenifar A: The comparison of anticancer activity of thymoquinone and nanothymoquinone on human breast adenocarcinoma. Iran J Pharm Res, 14(2), 539–46 (2015) [PubMed: 25901162].

[35] Motaghed M, Al-Hassan FM and Hamid SS: Thymoquinone regulates gene expression levels in the estrogen metabolic and interferon pathways in MCF7 breast cancer cells. Int J Mol Med, 33(1), 8–16 (2014) DOI: 10.3892/ijmm.2013.1563 [PubMed: 24270600].

[36] Odeh F, Ismail SI, Abu-Dahab R, Mahmoud IS and Al Bawab A: Thymoquinone in liposomes: a study of loading efficiency and biological activity towards breast cancer. Drug Deliv, 19(8), 371–7 (2012) DOI: 10.3109/10717544.2012.727500 [PubMed: 23043626].

[37] Woo CC, Hsu A, Kumar AP, Sethi G and Tan KH: Thymoquinone inhibits tumor growth and induces apoptosis in a breast cancer xenograft mouse model: the role of p38 MAPK and ROS. PLoS One, 8(10), e75356 (2013)DOI:10.1371/journal.pone.0075356 [PubMed: 24098377].

[38] Sutton KM, Greenshields AL and Hoskin DW: Thymoquinone, a bioactive component of black caraway seeds, causes G1 phase cell cycle arrest and apoptosis in triple-negative breast cancer cells with mutant p53. Nutr Cancer, 66(3), 408–18 (2014) DOI:10.1080/01635581.2013.878739 [PubMed: 24579801]

[39] Woo CC, Loo SY, Gee V, Yap CW, Sethi G, Kumar AP and Tan KH: Anticancer activity of thymoquinone in breast cancer cells: possible involvement of PPAR-gamma pathway. Biochem Pharmacol, 82(5), 464–75 (2011) DOI: 10.1016/j.bcp.2011.05.030 [PubMed: 21679698]

[40] Rajput S, Kumar BN, Dey KK, Pal I, Parekh A and Mandal M: Molecular targeting of Akt by thymoquinone promotes G(1) arrest through translation inhibition of cyclin D1 and induces apoptosis in breast cancer cells. Life Sci, 93(21), 783–90 (2013) DOI: 10.1016/j.lfs.2013.09.009 [PubMed: 24044882]

[41] M. Athar, J. H. Back, L. Kopelovich, D. R. Bickers, and A. L. Kim,"Multiple molecular targets of resveratrol: Anti-carcinogenic mechanisms," Archives of Biochemistry and Biophysics, vol. 486,no. 2, pp. 95–102, 2009.

[42] J. F. Savouret and M. Quesne, "Resveratrol and cancer: a review,"Biomedicine & Pharmacotherapy, vol. 56, no. 2, pp. 84–87, 2002.

[43] Carter LG, D'Orazio JA and Pearson KJ: Resveratrol and cancer: focus on in vivo evidence. Endocr Relat Cancer, 21(3), R209–25 (2014) DOI: 10.1530/erc-13-0171 [PubMed: 24500760].

[44] Kala R, Shah HN, Martin SL and Tollefsbol TO: Epigenetic-based combinatorial resveratrol and ptero-stilbene alters DNA damage response by affecting SIRT1 and DNMT enzyme expression, including SIRT1-dependent gamma-H2AX and telomerase regulation in triple-negative breast cancer. BMC Cancer, 15, 672 (2015) DOI: 10.1186/s12885-015-1693-z [PubMed: 26459286].

[45] Vinod BS, Nair HH, Vijayakurup V, Shabna A, Shah S, Krishna A, Pillai KS, Thankachan S and Anto RJ: Resveratrol chemosensitizes HER-2-overexpressing breast cancer cells to docetaxel chemoresistance by inhibiting docetaxel-mediated activation of HER-2-Akt axis. Cell Death Discov, 1, 15061 (2015) DOI: 10.1038/cddiscovery.2015.61 [PubMed: 27551486].

[46] Sprouse AA and Herbert BS: Resveratrol augments paclitaxel treatment in MDA-MB-231 and paclitaxel-resistant MDA-MB-231 breast cancer cells. Anticancer Res, 34(10), 5363–74 (2014) [PubMed: 25275030].

[47] Casanova F, Quarti J, da Costa DC, Ramos CA, da Silva JL and Fialho E: Resveratrol chemosensitizes breast cancer cells to melphalan by cell cycle arrest. J Cell Biochem, 113(8), 2586–96 (2012) DOI: 10.1002/jcb.24134 [PubMed: 22415970].

[48] Fan P, Fan S, Wang H, Mao J, Shi Y, Ibrahim MM, Ma W, Yu X, Hou Z, Wang B and Li L: Genistein decreases the breast cancer stem-like cell population through Hedgehog pathway. Stem Cell Res Ther, 4(6), 146 (2013) DOI: 10.1186/scrt357 [PubMed: 24331293].

[49] F. H. Sarkar and Y. Li, "Soy Isofavones and Cancer Prevention," Cancer Investigation, vol. 21, no. 5, pp. 744–757, 2003.

[50] Li Y, Meeran SM, Patel SN, Chen H, Hardy TM and Tollefsbol TO: Epigenetic reactivation of estrogen receptor-alpha (ERalpha) by genistein enhances hormonal therapy sensitivity in ERalpha-negative breast cancer. Mol Cancer, 12, 9 (2013) DOI: 10.1186/1476-4598-12-9 [PubMed: 23379261].

[51] Latocha M, Plonka J, Kusmierz D, Jurzak M, Polaniak R and Nowosad A: Transcripional activity of genes encoding MMPs and TIMPs in breast cancer cells treated by genistein and in normal cancer-associated fibroblasts--in vitro studies. Acta Pol Pharm, 71(6), 1095–102 (2014) [PubMed: 25745786].

[52] Xie Q, Bai Q, Zou LY, Zhang QY, Zhou Y, Chang H, Yi L, Zhu JD and Mi MT: Genistein inhibits DNA methylation and increases expression of tumor suppressor genes in human breast cancer cells. Genes Chromosomes Cancer, 53(5), 422–31 (2014) DOI: 10.1002/gcc.22154 [PubMed: 24532317].

[53] Pan, H.; Zhou, W.; He, W.; Liu, X.; Ding, Q.; Ling, L.; Zha, X.; Wang, S. Genistein inhibits MDA-MB-231 triple-negative breast cancer cell growth by inhibiting NF-κB activity via the Notch-1 pathway. Int. J. Mol. Med. 2012, 30, 337–343.

[54] Li, Z.; Li, J.; Mo, B.; Hu, C.; Liu, H.; Qi, H.; Wang, X.; Xu, J. Genistein induces cell apoptosis in MDA-MB-231 breast cancer cells via the mitogen-activated protein kinase pathway. Toxicol. In Vitro 2008, 22, 1749–1753.

[55] Rajah, T.T.; Du, N.; Drews, N.; Cohn, R. Genistein in the presence of 17beta-estradiol inhibits proliferation of ERbeta breast cancer cells. Pharmacology 2009, 84, 68–73.